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TOWNSEND and TOWNSEND and CREW LLP

By:_____

PATENT
Attorney Docket No.: 20833-003000US
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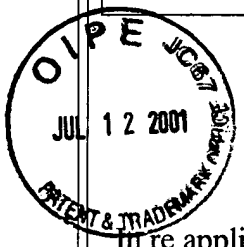

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Raja G. Achari, et al.

Application No.: 09/334,537

Filed: June 16, 1999

For: PHARMACEUTICAL FORMULATIONS AND METHODS COMPRISING INTRANASAL MORPHINE

Examiner: S. Wang

Art Unit: 1617

DECLARATION OF DR. STEVEN C. QUAY UNDER 37 CFR 1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Dr. Steven C. Quay, declare and state as follows:

1. I am currently the President and CEO for Nastech Pharmaceutical Company Inc., (the "Company"), the assignee of the above-identified patent application.

2. I have been employed by the Company since August 2000 as the Company's Chairman, President and Chief Executive Officer. In 1999, I founded and was Chairman, President and CEO of Atossa Healthcare, Inc., which focused on the development of a proprietary platform of diagnostics and treatments related to breast cancer risk assessment and therapeutics and other women's health care products. Atossa was acquired by Nastech in August 2000. In 1991, I founded SONUS Pharmaceuticals, Inc., a company engaged in the research and development of drug delivery systems and oxygen delivery products based on its

emulsion and surfactant technology, where I served as Chief Executive Officer, President and a director until June 1999. In 1984, I founded Salutar, Inc. to develop contrast agents for magnetic resonance imaging. Two pharmaceuticals, OmniScan(R) and TeslaScan(R) were invented by me at Salutar and are now FDA-approved for sale in the United States and other countries.

3. I graduated from the University of Michigan Medical School, where I received a M.A. and Ph.D. in Biological Chemistry in 1974 and 1975, respectively. I was awarded the Rackham Research Award for medical research. I conducted post-graduate research in the chemistry department at the Massachusetts Institute of Technology, and received my residency training at the Massachusetts General Hospital, Harvard Medical School. From 1980 to 1986 I was a faculty member at Stanford University School of Medicine. I have authored more than 100 papers in diagnostic imaging, oncology and biochemistry and have received 40 US patents. I am a member of numerous professional societies, including the American Society for Biochemistry and Molecular Biology, the Society of Magnetic Resonance in Medicine, the American Society for Echocardiology, and the American Institute for Ultrasound Medicine. My Curriculum Vitae is attached hereto as Appendix A.

4. I have read and fully understand the specification and claims of the above-identified patent application. I have also reviewed and fully understand the substantive Office Actions in the application, identified as Paper No. 6, dated November 26, 1999, and Paper No. 10, dated January 9, 2001, as well as the disclosures and claims of the references cited in the Office Actions, namely the patents to Merkus (U.S. Patent No. 5,756,483 ('483) and U.S. Patent No. 5,942,251 ('251)), and to Hussain (U.S. Patent No. 4,464,378 ('378) or WO 82/03768).

5. The following facts and conclusions relate to the Hussain '378 patent cited by the Office (the '378 patent is equivalent in its relevant disclosure to the WO 82/03768 reference). In regard to this disclosure, the Office Action paper No. 6 states as follows:

> The prior art teaches a pharmaceutically acceptable nasal dosage form for nasally delivering systemically therapeutic levels of drug e.g., morphine to a warm-blooded animal. See page 5, lines 3-15 in the WO patent or column 2, lines 45-62 in the US patent. The WO patent teaches a 15 mg/0.1ml solution (15%) of morphine at pH 4.5. See page 22 example 2 in the WO patent or column 10, example 2 in the US patent.

5. I respectfully disagree with the Office's interpretation of the Hussain '378 patent. The '378 disclosure, viewed as a whole for what it teaches to an artisan of ordinary skill, and considering the state of knowledge in the art at the time of the invention, neither discloses nor suggests an intranasal morphine formulation as characterized by the Office (i.e., "a 15 mg/0.1ml solution (15%) of morphine at pH 4.5").

6. The cited passage of the Hussain '378 patent which is relied upon by the Office to support the rejection (Col 10, Example 2) would not have taught a skilled artisan to make an intranasal composition containing morphine with a pH of 4.5. As an initial point, the passage is principally directed to a protocol for preparing a solution of nalbuphine hydrochloride. This protocol includes several steps, recited as follows:

> 15 grams of nalbuphine hydrochloride are combined with 80 ml of distilled water and the pH is adjusted to 4.5 with dilute sodium hydroxide solution. A quantity of water sufficient to bring the total volume to 100 ml is then added and sufficient sodium chloride is added to adjust the solution to isotonicity. The solution is then sterilized by being passed through a 0.2 micron Millipore filter. The resultant composition contains 15 mg of nalbuphine hydrochloride per 0.1 ml.

7. Several critical points immediately come into question from my reading of the above passage. First of all, the step relating to pH adjustment to a value of 4.5 is conducted at an intermediate stage of the protocol, prior to the addition of water to reach final volume and the adjustment of tonicity by addition of sodium chloride. Accordingly, the passage should not be interpreted to teach a final pH of a nalbuphine hydrochloride solution.

Secondly, the protocol is not expressly matched for preparation of a morphine sulfate solution. This is clear from the statement in column 10, lines 45-49 that:

> The procedure above is substantially repeated, except that 15 grams of morphine sulfate are used in place of the nalbuphine hydrochloride, affording a nasal composition containing 15 mg of morphine sulfate per 0.1 ml.

8. To the artisan of ordinary skill, the term "substantially repeated" leaves open all unspecified conditions and parameters of the protocol to routine adjustment, particularly modifications aimed at tailoring the protocol to the specific characteristics of substitute compounds proposed for formulation according to the general protocol (e.g., morphine sulfate, and pentazocine lactate, each proposed as substitutes for nalbuphine hydrochloride). Among the most likely parameters that would be considered for change in this context is adjustment of pH for a morphine sulfate, versus nalbuphine hydrochloride, solution. Simply put, the artisan would not presume from the cited passage that the '378 disclosure teaches a final pH of 4.5 for a morphine sulfate solution, even if one accepts the Office's position that the passage actually teaches this value for a nalbuphine hydrochloride solution. On the contrary, the artisan would more likely interpret the express qualification conveyed by the term "substantially repeated" in the passage, to leave the protocol open to such desired modifications as compound-specific pH adjustment. This interpretation is further supported by knowledge in the art regarding the specific physicochemistry of morphine, discussed below.

9. It was widely understood at the time of the invention that the degree of ionization of a drug influences the drug's ability to be delivered systemically across mucosal surfaces. The degree of ionization of a particular drug is largely determined by the drug's dissociation constant, the pKa, and the pH of the solution in which the drug is dissolved (The pKa of an acid is equal to the pH at which half of the molecules are ionized and half are neutral). A basic drug would be mostly in its unionized state when dissolved in a solution having a pH greater than the pKa of the drug. Accordingly, basic drug formulations are believed to be best absorbed from alkaline solutions where the pH is greater than the drug's

pKa. In the particular case of intranasal formulation chemistry, it was a widely known teaching in the art that basic drugs generally show improved absorption across the nasal mucosa into the bloodstream when they are formulated in a basic solution having a pH greater than the dissociation constant of the drug. Therefore, for morphine formulations where the subject drug is a basic drug having a pKa of about 8.0, the artisan would generally have predicted the drug to be best absorbed when formulated in a basic solution, wherein the morphine would be delivered predominantly in its unionized state.

10. Following this reasoning, the artisan would generally consider that solutions of morphine sulfate having a final formulation pH of greater than about 7.0 or 8.0 would allow for better absorption of morphine than lower pH solutions. For example, approximately 90% of the morphine sulfate in a solution having a final pH of about 9.0 would be expected to be in the preferred, unionized state (i.e., morphine free base). On this basis, such a high pH solution would be expected to provide for good absorption of morphine from the solution. In contrast, approximately 99% of the morphine would be predicted to be in an ionized state in a morphine sulfate solution having a pH of 6.0. A person of ordinary skill in the art generally would not have expected that morphine having such a high ionization level would provide for adequate absorption of the drug across the nasal mucosa into the bloodstream. The finding in the present invention that there is a high level of morphine absorption into the bloodstream when administered in formulations at pH 6.0 was therefore unexpected, and is clearly neither disclosed nor suggested by the art of record in the application. Similar results were shown for morphine sulfate at a pH range of about 3.0 to about 5.0, where over 99% of the morphine is also in an ionized state.

11. Yet additional teachings of the Hussain '378 patent clearly evince that this reference fails to disclose or suggest the presently claimed morphine solutions. In fact, the protocol described by Hussain (for nalbuphine hydrochloride) could not be followed to yield a solution of morphine sulfate in the manner proposed by the Office. To illustrate this fact, the Hussain protocol for nalbuphine hydrochloride teaches to combine 15 grams of nalbuphine hydrochloride with 80 ml of water, then add enough sodium hydroxide solution to bring the pH of the composition to 4.5, then bring the solution to 100 ml with water. The statement in the

'378 patent (Col. 10, Lines 45-49), that this procedure "is substantially repeated, except that 15 grams of morphine sulfate are used in place of the nalbuphine hydrochloride", teaches an inoperable protocol, and therefore cannot be interpreted in the strict manner proposed by the Office (Note: that the Office itself directly cites the Hussain '378 patent as teaching a morphine sulfate composition "containing 15 mg of morphine sulfate per 0.1 ml of water.") The flaw in this interpretation of the '378 patent teachings is clearly revealed by the fact that the solubility of morphine sulfate in water would need to be at least approximately 150 mg/ml to achieve the formulation proposed by the Office (by "substantial" subsitution following the actual, nalbuphine hydrochloride procedure). This solubility is grossly overestimated, and cannot be achieved under normal conditions at any pH. This defect is clearly elucidated by the following experiments conducted under my direction and reported herein as follows:

A. Preparation of a Morphine Sulfate Solution Following Example 2 of U.S. 4,464,378 (as construed by the Office).

15 grams of morphine sulfate were mixed with 80 mL of water. The pH of the mixture was adjusted to 4.5 with dilute NaOH and stirred for two hours. The volume of the solution was made up to 100 mL with water.

Result: A clear solution was not obtained, indicating that 15 gm/mL of morphine sulfate is not soluble following the foregoing procedure, including intermediate adjustment of the 80 ml solution to pH 4.5.

B. Evaluation of Actual Solubility of Morphine Sulfate in an Aqueous Solution, Before and After pH Adjustment.

i) To estimate the true drug solubility for morphine sulfate in an aqueous solution, the drug was added to water in small increments of about 0.5 gm each to obtain a saturated solution. After the solution was thus prepared, the volume of the solution was made up to 100 mL, and sufficient NaCl was added to adjust the solution to isotonicity (see, Example 2 of '378 patent directed to preparation of nalbuphine hydrochloride solution).

Result: The characteristics of the saturated aqueous formulation at 80 ml were as follows:

Water = 80 mL

Morphine Sulfate added: 4.342 gm + 0.529 gm

NaCl added: 0.218 gm (calculated based on total amount of Morphine Sulfate added.)

These findings indicate that the estimated solubility of morphine sulfate in water is about 50 mg/mL.

ii) Following this study, the pH of the morphine sulfate solution set forth in subsection i), above, was adjusted to 4.5, in order to determine the effects, if any, that the pH adjustment would have on solubilization of the morphine sulfate (saturated as indicated at about 50 mg/ml in the non-pH-adjusted solution). To assess this factor, the pH of the solution was adjusted incrementally by slow, stepwise addition of NaOH. After each addition of NaOH, the mixture was stirred for 30 min.

Result: A clear solution of morphine sulfate from the solution set forth in subsection i), above, was not achieved at any elevated pH up to pH 8.12.

12. The foregoing comparative experimental findings clearly demonstrate that the prophetic disclosure of the Hussain '378 patent regarding the preparation of a morphine sulfate solution (as strictly construed by the Office) is impracticable. This demonstration casts serious doubt upon all of the teachings of this reference pertaining to morphine formulations, including the desired pH of such formulations for intranasal use, as these teachings have been interpreted by the Office. The prophetic suggestion to make a blanket substitution of morphine sulfate for nalbuphine hydrochloride in a slavishly copied protocol, which is contrary to the skilled artisan's interpretation of the disclosure for the reasons noted above, renders an inoperable formulation. Because it is impossible to obtain a morphine sulfate solution "containing 15 mg of morphine sulfate per 0.1 ml of water", there

can be no valid scientific significance assigned to any disclosure of a particular pH value of such an impracticable solution.

13. Considering the foregoing evidence regarding the teachings of the Hussain '378 patent in regard to the pH of intranasal morphine formulations, the skilled artisan would ordinarily have looked for additional information, in the patent and elsewhere in the art, to determine a desired pH for such a solution. In this regard, my experience leads me to the conclusion that the artisan would ordinarily have selected a considerably higher pH, e.g., greater than 7.0 or 8.0, in light of the knowledge summarized above concerning the pKa of morphine and the desirability of delivering drugs across mucosal surfaces in an unionized state. Further supporting this selection, it is particularly noteworthy that the Hussain '378 patent provides the following disclosure (Example 5, at columns 11-12) in particular reference to aqueous intranasal formulations:

> The following are illustrative aqueous solutions of selected drugs suitable for use as nasal drops or nasal spray. In each case, the pH of the final composition is adjusted to 7.4 . . .. (emphasis added).

14. The first identified composition in this Example ("COMPOSITION A") is an aqueous intranasal formulation of nalbuphine hydrochloride. The teaching that the final pH of this nalbuphine composition is to be adjusted to pH 7.4, rather than pH 4.5, is facially inconsistent with the Office's interpretation of the protocol described in Example 2 of this reference, discussed above, and is consistent with my conclusion that the teachings regarding pH adjustment in Example 2 fail to convey a desired final pH adjustment to 4.5—for either a nalbuphine or morphine intranasal formulation.

15. Regarding the Merkus references cited by the Office (U.S. Patents: 5,756,483 and 5,942,251), these references also fail to teach or suggest an effective, nasally-administered morphine composition having a specific pH (pH 6.0) as advocated by the Office. On the contrary, the teachings of these two patents (which are also equivalent in their relevant

disclosures) lead directly away from the proposed formulation of morphine sulfate having a pH within the present claims.

16. As a preliminary point, I note that the teachings of Merkus that are relied upon by the Office are not in fact part of the disclosures of the cited patents. On the contrary, the cited teachings are discussed in Merkus as a previous attempt by others (Verweij et al.) to formulate intranasal morphine. The cited Dutch study yielded undesired results, which are directly criticized and distinguished in the Merkus disclosures. Consequently, it appears that the Merkus reference is relied on improperly as the source of the supposed teachings regarding morphine solutions having a pH of 6.0. Additionally, it is respectfully submitted that the Merkus disclosures were misinterpreted as embracing the teachings from the Dutch study, when in fact the study is presented as a failed attempt by others that therefore teaches away from the presently claimed subject matter.

17. Referring to the cited passages of Merkus in more detail, the '483 disclosure states in column 6, lines 37-41 as follows:

> To overcome the drawbacks of the oral and parenteral routes of administration of morphine, the use of a nasal spray has been proposed (S.L. Verweij and R. van Gijn; Can morphine be administered nasally? Ziekenhuisfarmacie (Dutch) 1988; 4: 73-77.

18. The Merkus patents next cite the composition of the nasal solution from the Dutch study, which includes the notation "phosphate buffer (0.01 mol/L; pH 6.0)." Notably, this notation specifies the pH of the phosphate buffer, not of the final formulation achieved by inclusion of the buffer.

19. In further discussing the Dutch study, the Merkus '483 disclosure directly criticizes and distinguishes the results of the study, as follows:

> [T]he bioavailability of morphine after giving the nasal spray as described by Verweij and van Gijn is relatively low. After nasal absorption there is no first pass effect and therefore the nasal bioavailability should be higher than the oral.

20. However, the bioavailabilty of morphine delivered intranasally according to the Dutch disclosure was even lower than the oral bioavailability, which is also noted by Merkus with skepticism. Clearly, the Merkus disclosures then do not teach an effective intranasal morphine solution having a pH of 6.0 as advocated by the Office. On the contrary, Merkus is not even the actual source of information on which the Office's conclusions are based, and the Merkus disclosure directly criticizes and distinguishes the foundational study. Accordingly, the Merkus disclosures actually teach away from any disclosure in the Dutch reference regarding effective pH values for intranasal morphine solutions. Based on the Merkus disclosure, nasally-administered morphine compositions including a phosphate buffer with a pH of 6.0 yield a morphine bioavailability that is substantially lower than the bioavailability of orally-administered morphine. On this basis, the skilled artisan would have been taught to administer morphine compositions orally, not nasally, and would have been guided away from using nasally-administered morphine compositions incorporating a buffer designated to have a pH of 6.0.

21. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that I make these statements with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize validity of the application or any patent issuing thereon.

Date: 9 July 2001 By: 
Dr. Steven C. Quay